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Review

Novel Sjögren's autoantibodies found in fibromyalgia patients with sicca and/or xerostomia

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A B S T R A C T

Introduction: A significant proportion of patients with fibromyalgia (FM) complain of dry eyes and mouth. Many Sjögren's syndrome (SS) patients also complain of FM symptoms, and there is literature that suggests that there is interplay between these two disorders. Recently, the presence of novel tissue specific autoantibodies (TSAs), SP-1, CA6, and PSP, has been observed in the early stages of SS. These early markers present themselves before the classic autoantibodies, such as SS-A/Ro, SS-B/La, ANA, and RF.

Objective: This study aims to examine the relationship between SS and FM by testing patients with FM who also complain of xerostomia and sicca symptoms, for SS-related biomarkers.

Methods: A cohort of 185 patients who met both the 1990 and 2010 preliminary diagnostic criteria for FM and who admitted to symptoms of sicca and/or xerostomia were selected for this study. Serum from 151 study patients was sent to a tertiary lab, Immco Diagnostics, for testing of the classic autoantibodies (SS-A/Ro, SS-B/La, ANA and RF) and TSAs (SP-1, CA6, PSP), while the rest (34 patients) were tested for TSAs only.

Results: Of the 151 patients who were evaluated for both the early and classic SS markers, 49 (32%) tested positive for SS autoantibodies. Of those, 4 (3%) tested positive for the classic SS markers only, 40 (26%) of the patients tested positive for the early SS markers only, and 5 (3%) tested positive for both the early and classic SS markers. Of the 34 patients who were tested for early SS markers only, 10 (29%) tested positive and 24 (71%) tested negative. Further analysis of all the patients that tested positive for the TSAs (n = 55), found 83.6% (46) were positive for SP-1, 12.7% (7) were positive for CA6 and 20.0% (11) were positive for PSP. 85.5% (47) of these patients were positive for only one of the TSAs and 14.5% (8) were positive for more than one TSA.

Conclusion: Approximately 1/3 of FM patients that were tested for both the TSAs and classic Sjögren's markers tested positive for a SS biomarker, and the majority of those patients tested positive for one or more of the TSAs. This suggests that autoimmunity, specifically early- stage Sjögren's syndrome, may be involved in the pathophysiology of fibromyalgia.

1. Introduction

Fibromyalgia (FM) is a common cause of chronic, widespread, musculoskeletal pain [1,2] that affects 6 times more women than men [3]. In fact, FM is the most common cause of musculoskeletal pain in women between the ages of 20 and 55 years [3]. FM is clinically diagnosed according to the 1990 and/or 2010 preliminary American College of Rheumatology criteria (Table 1) [4,5]. Patients often also present with fatigue [6], cognitive disturbances including issues with attention, otherwise known as “fibrofog” [7], frequent headaches [8,9], paresthesias in both arms and legs, such as numbness, tingling, and burning [10], ocular dryness [11], and dry mouth [5]. Comorbidities of FM include depression, irritable bowel syndrome, chronic fatigue syndrome, temporomandibular disorder, sleep disorders [12], inflammatory rheumatic diseases [13], and Raynaud- like phenomenon [12]. FM is a diagnosis of exclusion, and can be differentiated from connective tissue, inflammatory, and neurological disorders, as well as other causes of myalgia and myopathies, with bloodwork and a thorough history and physical examination [14].

Numerous FM studies have provided evidence supporting physical manifestations of the condition, beyond patient- reported symptomology. For example, neurochemistry studies of FM patients have shown a reduction in *N*- acetylaspartate in the hippocampus [15], suggesting hippocampal dysfunction [16]. Elevation of excitatory compounds including substance P [17], nerve growth factor, and brain-derived neurotrophic factor [18], which can lead to activation of the neuroinflammatory response, and reduction in inhibitory neurotransmitter gamma-aminobutyric acid (GABA), have also been found in studies of FM patients [17]. Additionally, hypo-reactivity of the autonomic nervous system has been indicated [12]. There is evidence that FM may even impact patients' endocrine system; they have lower levels of growth hormone [19] and insulin-like growth factor 1 (IGF-1) [20], compared to healthy controls.

FM does not have a cure, and is primarily treated via symptom

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Table 1
ACR 1990 and 2010 Classification Criteria for FM.

1990 criteria
1 Chronic widespread pain for at least 3 months above and below the waist and on both sides of the body, and pain in the axial skeleton 2 Pain induced by palpation with approximately 4 kg/cm^2 force, in at least 11 of 18 tender points
2010 criteria
Consists of 2 parts 1) Widespread Pain Index (WPI) = the total number of body area that have been painful for the patient during the past week (0–19 body areas) 2) Symptom Severity Scale (SSS) = the summation of the following 2 components for a total score of 0–12: a) Patient rating of three somatic symptoms: waking unrefreshed, disturbed cognition, and fatigue (scale 0–3 each, for a total of 0–9) b) Patients choose from a list of 41 somatic symptoms experienced over the past week, and the physician numerically judges the number of symptoms from no symptoms (0) to a great deal of symptoms [3]
Criteria for Diagnosis 1 WPI ≥ 7 and SS ≥ 5, or WPI 3–6 and SS ≥ 9. 2 Symptoms have been consistently present at a similar level for at least 3 months. 3 No other disorder present that would otherwise explain the symptoms.

management. However, treatment is often difficult because the pathogenesis of FM is currently unknown. One possibility is an unrecognized, underlying autoimmune process. This may explain why many patients with this illness often also have autoimmune markers such as elevated ANA levels [21]. In previous studies, FM has been identified in up to 65% of systemic lupus erythematosus patients [22], 57% of rheumatoid arthritis patients, 24% of psoriatic arthritis patients [23] and 62% of patients with Hashimoto's thyroiditis [24].

Sicca and xerostomia are common presenting symptoms of FM, and are included as part of the Somatic Severity Scale in the 2010 preliminary FM diagnostic criteria [5]. Sicca and xerostomia are also the primary symptoms of Sjogren's syndrome (SS), an associated inflammatory autoimmune process [25].

SS is characterized by lymphocytic infiltration of the lacrimal and salivary glands [26] that can produce a broad spectrum of disease, ranging from dry eyes, dry mouth, and body aches to small nerve pathology and peripheral neuropathy [27]; common presentations that mimic FM. The diagnostic criteria of SS (Table 2) [25] include the presence of anti-Ro/SS-A autoantibodies, and diagnosis is confirmed with a glandular biopsy. SS is often associated with other autoimmune conditions, such as rheumatoid arthritis and systemic lupus erythematosus [26].

When following the strict diagnostic criteria, SS is often diagnosed late, when the effected glands are already destroyed or nonfunctional [28]. Recently, the presence of novel tissue specific autoantibodies (TSAs), SP-1, CA6, and PSP, has been observed in the early stages of SS [29]. A study found that 76% of patients with idiopathic xerostomia and exophthalmia for < 2 years were positive for the TSAs, while only 31% had antibodies to SS-A/Ro and SS-B/La. The same study also found that in a group of 20 patients who met full diagnostic criteria for SS, including positive salivary gland biopsies, but lacked Ro/La autoantibodies, 45% were positive for SP-1. The authors concluded that SP-1, CA6, and PSP present themselves before the classic autoantibodies, such as Ro, La, ANA, and RF, and may therefore be useful markers for identifying patients with SS at an early stage of the disease, before destruction of the glands [29].

Table 2
American College of Rheumatology/European League Against Rheumatism Classification Criteria for Primary Sjogren's Syndrome (2016).

Individuals with signs and/or symptoms suggestive of SS who have a **score of ≥ 4** when the following components are totaled
- Anti-SSA/Ro antibody positivity and focal lymphocytic sialadenitis with a focus score of ≥1 foci/4 mm2, each scoring 3 - An abnormal ocular staining score of ≥5 (or van Bijsterveld score of ≥4) - A Schirmer's test result of ≤5 mm/5 min, and an unstimulated salivary flow rate of ≤0.1 ml/min, each scoring 1

Previous studies have shown overlapping symptomatology between FM and SS including fatigue, tender points [30], sicca and xerostomia [31]. A 1995 study tested a cohort of 28 FM patients with abnormal Schirmer tests (< 15 mm in 5 min) for SS, resulting in 5 positive salivary gland biopsies and 2 patients with positive Ro/La autoantibody tests [31]. In another study, a 22% rate of FM was found in a cohort of 100 patients with primary Sjögren's syndrome, compared to 3.3% in healthy controls [32].

This retrospective study aims to examine the relationship between FM and SS by testing FM patients, who report xerostomia and sicca symptoms, for SS- related autoantibodies. Screening for novel, early TSAs, in addition to the classic Ro/La autoantibodies, reveals the presence of SS in FM patients that may have been undiagnosed in previous studies. The discovery of SS biomarkers in this large cohort of FM patients could provide evidence supporting the role that autoimmunity may play in the pathogenesis of FM.

2. Methods

A cohort of 185 patients, 93% female and 7% male, with an average age of 55 years, was identified that presented with symptoms of fibromyalgia, meeting both the 1990 and 2010 preliminary criteria. These patients were further questioned about xerostomia and sicca symptoms. Patients who admitted to using artificial tears at least biweekly, drinking water excessively to relieve dry mouth, but did not have previously established SS and did not have elevated inflammatory markers (ie. ESR, CRP, or elevated globulins), were selected for this study. Serum from 151 study patients was sent to a tertiary lab, Immco Diagnostics early on in the study, and later, Quest and Labcorp, for testing of the classic autoantibodies (Ro, La, ANA, RF) and TSAs (SP-1, CA6, PSP) markers, while the rest (34 patients) were tested for TSAs only. Patients testing positive for the TSA markers were provided with literature on the disease and offered appropriate treatment options, such as hydroxychloroquine.

3. Results

Of the 151 patients who were evaluated for both the early and classic SS markers, 49 (32%) tested positive for SS autoantibodies (Fig. 1). Of those, 4 (3%) tested positive for the classic SS markers only, 40 (26%) of the patients tested positive for the early SS markers only, and 5 (3%) tested positive for both the early and classic SS markers. Of

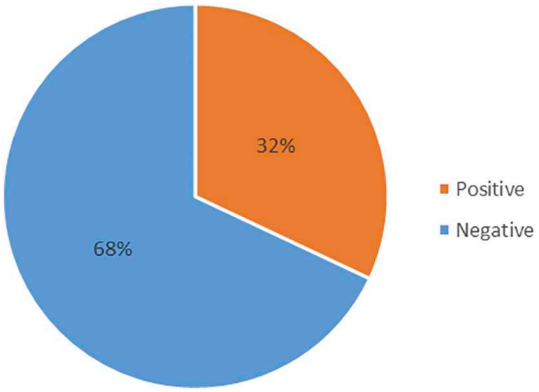

Fig. 1. About a third of FM patients tested positive for either early or classic SS antibodies when evaluated for all biomarkers.

the 34 patients who were tested for early SS markers only, 10 (29%) tested positive and 24 (71%) tested negative. Further analysis of all the patients that tested positive for the TSAs (n = 55), found 83.6% [46] were positive for SP-1, 12.7% [7] were positive for CA6 and 20.0% [11] were positive for PSP. 85.5% [47] of these patients were positive for only one of the TSAs and 14.5% [8] were positive for more than one TSA.

4. Discussion

The results of the present study show that roughly a third of FM patients with symptoms of dry eyes and/or dry mouth tested positive for at least one SS biomarker. This provides compelling evidence in favor of a correlation of SS and FM, which may provide insight into the involvement of autoimmunity in the pathogenesis of FM.

Our conclusion regarding FM and autoimmunity is also consistent with recent studies involving Chronic Fatigue Syndrome (CFS). CFS is characterized by severe, debilitating fatigue, and overlaps heavily with FM in other symptomology, such as perpetual exhaustion, chronic pain of unknown etiology, and autonomic dysfunction [33]. In fact, up to 77% of patients who fulfill disease criteria for CFS also meet the criteria for FM [34], and anti-68/48 kD antibodies are considered to be closely associated with both FM and CFS patients who present with hypersomnia or cognitive disorders, suggesting a common immunologic etiology [35]. Although the exact pathogenesis of CFS is unclear, just as in FM, many autoantibodies, mostly against nuclear and membrane structures [36], as well as neurotransmitter receptors [37], have been identified. The depletion of these autoantibodies via B cell depleting therapy (rituximab) provided clinical benefit to 67% of CFS patients, versus 13% control, suggesting an autoimmune pathogenesis [38].

The detection of early SS TSAs may play an important future diagnostic role in SS, in order to identify and treat SS before the lacrimal and salivary glands are destroyed. Interestingly, a handful of our subjects with FM and dry eye/mouth, who tested positive for TSAs, have shown a general trend of decreasing TSA levels and clinical symptoms after treatment with hydroxychloroquine and repeated SS panels. A larger number of patients who have begun hydroxychloroquine therapy will be assessed in the future for a possible statistical significance of this pattern, and to confirm that antibody levels are indeed directly correlated with clinical symptoms such as body pain, sicca, and xerostomia.

Hydroxychloroquine (HCQ) was chosen because of its relative safety, as well as its prior use in the treatment of SS and other related autoimmune disorders. The clinical effect of HCQ was investigated in a double-blind, placebo- controlled trial of 120 patients with low disease activity (EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) median of 2.5) [39,40]. HCQ did not improve most of their symptoms, including eye dryness, mouth dryness, arthralgias, general pain, and fatigue, but there was a trend of reduced ESR, IgM, and IgG. However, this study, as well as similar, older studies, began HCQ treatment in the later stages of SS, several years after an official diagnosis of SS, or in patients with chronic active disease.

We believe that HCQ has the potential to ameliorate the earliest signs of disease, especially the earliest immune dysfunction. HCQ alters endocytic pH, which may affect cytokine production, resulting in reduced levels of pro-inflammatory IL-1 and TNF [41]. HCQ was also shown, by Wallace et al., to be associated with suppression of IL-6 in patients with SLE [42]. Importantly, HCQ inhibits Toll Like Receptor (TLR)-mediated immune responses, and therefore inhibits other pro-inflammatory cytokines [42].

HCQ has also been shown to significantly decrease cholinesterase activity, which can reverse the diminished production of saliva and gland hypofunction [43]. Treatment with HCQ also resulted in reduced levels of MXA, a biomarker of interferon type 1 activity, compared to those who were untreated. The interferon signature has been shown to be of prime importance in the development of SS [44].

Excessive production of interferon alpha has been associated with abnormal expression of the cytokine BAFF (B cell Activator Factor), which is involved in the formation of germinal centers, and subsequent B cell proliferation and differentiation, in SS [45,46]. A positive correlation has also been shown between the presence of SS-A antibodies and serum BAFF levels [47], and there have been studies associating BAFF levels and patients' progression and treatment of SS [48]. The correlation between SS TSAs and BAFF levels has yet to be studied. Elevated levels of BAFF have also been seen in a subset patients with CFS, as compared to controls [49].

The present study included a subjective analysis of symptoms and lacked controls. Plans for a future study are in place to address these shortcomings. We will be assessing lacrimal gland function via the Schirmer Test and possibly examining the integrity of the ocular surface via Lissamine green dye, in addition to more standardized subjective analyses, including the Ocular Surface Disease Index (OSDI) questionnaire [50]. Salivary hypofunction will be performed by measuring unstimulated salivary flow rate via a whole sialometry test. This study will also involve a healthy control group that matches the age range and genders of the patient cohort.

5. Conclusion

This retrospective study demonstrates a link between FM patients who demonstrate sicca and xerostomia symptoms, and SS, by means of recently available testing for tissue specific antibodies in patients with SS. This linkage suggests the possibility that autoimmunity plays a role in the pathogenesis of FM, which could potentially modify the paradigm of treatment for FM to include medications which affect the immune system, such as hydroxychloroquine. A future, larger study will seek to determine the efficacy of hydroxychloroquine in these patients by evaluating them both clinically and serologically. Another study with more objective measures, as well as a control group, is in progress to further verify the validity of our findings.

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